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International application number: PCT/EP05/002389

International filing date: 07 March 2005 (07.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: SI  
Number: P-200400073  
Filing date: 08 March 2004 (08.03.2004)

Date of receipt at the International Bureau: 21 March 2005 (21.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
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# P o t r d i l o

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(22) Datum prijave (*Application Date*):

8.3.2004 (8.mar.2004)

(21) Številka prijave (*Application No.*):

P-200400073

(54) Naziv (*Title*):

Kristalne oblike olanzapina in postopki za njihovo pripravo

Za izdajo tega potrdila je bila plačana taksa v višini 255,00 SIT po prvi alineji tarifne številke 4 taksne tarife Zakona o upravnih taksah (Uradni list RS, št. 8/00 in nadaljnji).

Ljubljana, 25.2.2005



Helena Zalaznik  
višja svetovalka I



## ZAHTÉVA ZA PODELITEV PATENTA

### 1. Naslov za obveščanje:

KRKA, d.d.

Služba za industrijsko lastnino

Šmarješka cesta 6

8501 Novo mesto

tel.: 07 3312 787

faks: 07 3321 572

šifra:

### Potrdilo o prejemu prijave (izpolni urad)

Datum vložitve prijave: 8. 3. 2004

Številka prijave: P-200400073

Žig urada in podpis:



Registrska številka:

### 2. Prijavitelj (priimek, ime in naslov, za pravne osebe firma in sedež):

KRKA, tovarna zdravil, d.d., Novo mesto

Šmarješka cesta 6

8501 Novo mesto

### 3. Zastopnik:

### 4. Izumitelj (priimek, ime in naslov):

navedeni v posebni prilogi

### 5. Naziv izuma:

Kristalne oblike olanzapina in postopki za njihovo pripravo

### 6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

### 7. Dodatne zahteve:


- ☐ prijava je za patent s skrajšanim trajanjem
- ☐ predhodna objava patenta po preteku \_\_\_\_\_ mesecev
- ☐ prijava je izločena iz prijave številka: \_\_\_\_\_

### 8. Izjava:

- ☐ izjava o skupnem predstavniku:

### 9. Priloge:

- ☒ opis izuma, ki ima 12 strani
- ☒ patentni zahtevek (zahtevki), ki ima(jo) 1 strani; število zahtevkov: 10
- ☒ skice (če so zaradi opisa izuma potrebne); število listov: 2
- ☒ povzetek
- ☐ potrdilo o plačilu prijave pristojbine
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- ☐ prikaz zaporedja nukleotidov ali aminokislin v opisu
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REPUBLIKA SLOVENIJA MINISTRSTVO ZA GOSPODARSTVO URAD RS ZA INTELEKTUALNO LASTNINO	
Prejeto dne: <u>08-03-2004</u>	Osebnostni oddelek: <input type="checkbox"/>
Podpis: _____	Oddano priporočeno dne: _____
Šifra: _____	Poštna številka: _____

Florjanič Mihael

Priimek in ime ter podpis prijavitelja (zastopnika)

Izumitelji so:

- 1.) Berta Kotar-Jordan  
Vodeniška 19  
8311 Kostanjevica na Krki
- 2.) Roman Lenaršič  
Tržaška cesta 266/B  
1000 Ljubljana
- 3.) Marija Grčman  
Mačji Dol 16  
8212 Velika Loka
- 4.) Matej Smrkolj  
Orehovica 4  
1411 Izlake
- 5.) Anton Meden  
Lukovica pri Domžalah 25  
1225 Lukovica
- 6.) Igor Simonič  
Potok 56  
8351 Straža
- 7.) Rok Zupet  
Janeza Rožiča 6  
1000 Ljubljana
- 8.) Jože Gnidovec  
Dobrava 47  
8222 Otočec

## Crystal forms of olanzapine and processes for their preparation

### FIELD OF THE INVENTION

The present invention belongs to the field of organic chemistry and relates to a new mixed solvate form of 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2,3-*b*] [1,5] benzodiazepine (hereinafter referred to by its generic name "olanzapine"), a method for production thereof, and a method for preparation of polymorphic form I of olanzapine.

Olanzapine has shown to have high activity with regard to the central nervous system and is also useful for the treatment of schizophrenia, schizophreniform disorders, acute mania, mild anxiety states and psychosis.

### TECHNICAL PROBLEM

According to prior art processes, solvents, like methylene chloride and acetonitrile, are used for the crystallization of form I of olanzapine but often they do not lead to satisfactory overall yields of the form I of olanzapine. Moreover, these prior art processes often do not lead to olanzapine having a purity which is satisfactory for the preparation of pharmaceutical formulations as impurities are present, which are hard to remove according to prior art processes.

Consequently, there is still a need for an improved process to prepare purified olanzapine avoiding the afore-mentioned drawbacks and which results to olanzapine which has a purity making it very well suitable for the preparation of pharmaceutical formulations.

Further, there is a need for precursors which allow the easy preparation of polymorphic forms of olanzapine or the conversion to other forms of olanzapine.

These problems are solved by the present invention.

### BACKGROUND OF THE INVENTION

The British patent GB 1 533 235 discloses antipsychotically effective thienobenzodiazepines by a generic formula which also covers olanzapine.

US patent 5,229,382 describes olanzapine explicitly. The described process for its synthesis further involves a crystallization from acetonitrile, determining the melting point of that crystallized compound at 195 °C.

EP-B-733 635 claims crystalline form II olanzapine and this polymorphic form is said to be more stable than the material obtained according to US 5,229,382 which is designated "form I olanzapine". Both the form I and the form II of olanzapine are characterized by e. g. X-ray data. The preparation of the more stable form II of olanzapine is effected by dissolving technical grade olanzapine in ethyl acetate and crystallization from the resulting solution by any conventional process such as seeding, cooling, scratching the glass of the reaction vessel or other common techniques.

WO 02/18390 discloses the monohydrate form I and the dihydrate form I of olanzapine, a process for production thereof and a process for production of form I of olanzapine which comprises the steps of stirring olanzapine monohydrate form I or crude olanzapine or form II of olanzapine in methylene chloride at reflux, cooling, filtering and drying. It is also described that a repeating of the process described in US 5,229,382 Example 1, subexample 4 did not lead to formation of form I of olanzapine.

WO 03/101997 relates to processes for preparation of form I of olanzapine by regulation of the pH-value of the solution.

WO 03/055438 discloses crystallization from ethanol and the consequent transformation of the ethanol solvate to polymorphic form I of olanzapine.

US patent US 5,637,584 discloses the (mono)methylene solvate form of olanzapine and a method for its conversion to polymorphic form I of olanzapine.

EP-B-733 634 relates to three specific solvates of olanzapine namely the methanol, ethanol and 1-propanol solvates and a process for production of form II olanzapine by drying the corresponding solvate.

In WO 03/097650 two new mixed solvate forms, the mixed water/methylene chloride and water/DMSO solvate, methods for preparing them, and their transformation to polymorphic form I are disclosed.

WO 04/006933 A2 discloses the preparation of preparation of form I, some pseudopolymorphic forms, namely isopropanol solvate, acetonitrile/methylene chloride/water and acetonitrile/water mixed solvates of olanzapine, polymorphic form A, and processes for the preparation thereof.

#### BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the ORTEP view of the asymmetric unit of  $C_{17}H_{20}N_4S \cdot H_2O \cdot \frac{1}{2}(C_3H_7OH)$ . Note that in Fig. 1 the population of disordered isopropanole molecule is 0.50.

Fig. 2 shows the NMR spectra of  $C_{17}H_{20}N_4S \cdot H_2O \cdot \frac{1}{2}(C_3H_7OH)$ .

#### SUMMARY OF THE INVENTION

The invention relates to a novel and well defined solvate form of olanzapine which is characterized by the x-ray structure in Figure 1 and by the NMR spectra in Figure 2 and which contains 2 molecules of water and one molecule of isopropanol per 2 molecules of olanzapine. The olanzapine water-isopropanol mixed solvate is prepared from the solvent mixture isopropanol/water.

It is preferred that the solvent mixture comprises isopropanol and water in a ratio of 9 to 1 parts, more preferably 20 to 1 and most preferably 35 to 1 by volume.

The olanzapine used as starting material can be in any form, e. g. it can be in reaction solution, crude, in filtrate, in anhydrous, solvated, or hydrated form, or mixtures thereof.

It has unexpectedly been found that the preparation of olanzapine water-isopropanol mixed solvate can easily be accomplished if olanzapine is crystallized by using the solvent mixture which comprises isopropanol and water. In this way persistent impurities are removed from the active compound and olanzapine can also be recovered from filtrates.

The process for the preparation of form I of olanzapine usually involves dissolving of olanzapine water-isopropanol mixed solvate in a solvent mixture which comprises methylene chloride, and then crystallizing and recovering the product by conventional processes.

By using the above crystallization conditions, it was possible to isolate form I of olanzapine from the olanzapine water-isopropanol mixed solvate form with yields, purity and quality which were improved in comparison with in prior art.

Form I of olanzapine is rather difficult to be prepared in substantially pure form, because formation of the thermodynamically more stable form II is favoured. According to the process of the present invention substantially pure form I free from form II and solvates could be obtained.

In the following preferred embodiments of the process are described.

#### DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a novel and well defined solvate form of olanzapine which is characterized by the x-ray structure in Figure 1 and by the NMR spectra in Figure 2 and which contains 2 molecules of water and one molecule of isopropanol per 2 molecules of olanzapine.

Single crystal x-ray diffraction data were collected at room temperature on a Nonius Kappa CCD diffractometer by means of the Nonius Collect Software. The structure was solved by using SIR97 (direct methods) and the refinement was performed with the X'tal software. The crystallographic data for the olanzapine isopropanol/water mixed solvate, particularly the interplanar distances (a, b, c) and angles ( $\alpha$ ,  $\beta$ ,  $\gamma$ ), are indicated in Table 1.

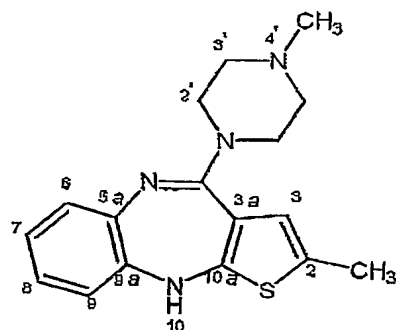
Table 1

Space group	C2/c (No. 15)
a	24.55 Å
b	12.51 Å
c	15.31 Å
$\alpha$	90°
$\beta$	125.3°
$\gamma$	90°

R	0.059
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NMR data were obtained on a Varian UNITY+ 300 (300 MHz) spectrometer, in  $\text{CDCl}_3$ , with tetramethylsilane as internal standard.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz) peak assignments:



$\cdot \text{H}_2\text{O} \cdot \frac{1}{2} (\text{CH}_3)_2\text{CHOH}$

Chemical shift $\delta$	Assignment
1.20 (3H, d)	$\text{CH}_3$ - isopropanol
2.30 (3H, s)	4'- $\text{CH}_3$
2.34 (3H, s)	2- $\text{CH}_3$
2.20-2.40 (2H, br s)	H - water
2.49 (4H, m)	3'- $\text{CH}_2$
3.52 (4H, m)	2'- $\text{CH}_2$
4.03 (0.5H, dq)	CH - isopropanol
5.02 (H, broad s)	10-NH
6.29 (H, broad s)	3-CH
6.29-7.05 (4H, m)	6,7,8,9-H

The olanzapine used as a starting material for the preparation of the described olanzapine water-isopropanol mixed solvate can be in any form, e. g. it can be used when it is contained in reaction solution, crude, in filtrate when various solvents are present, or in anhydrous or any solvated or hydrated form, or mixture thereof.



In the preferred embodiment the herein prepared and described olanzapine water-isopropanol mixed solvate is used for the preparation of highly pure form I of olanzapine, or any other solvated, hydrated or anhydrous form of olanzapine.

When the herein described olanzapine water-isopropanol mixed solvate is prepared from reaction mixture, a mixture of 4-amino-2-methyl-10H-thieno[2,3-b][1,5]benzodiazepine hydrochloride and 1-methylpiperazine is heated in high boiling solvents, as for example dimethylsulfoxide and toluene, or mixtures thereof, preferably under reflux, until the reaction is completed, preferably 3 to 12 hours. The solution is cooled, preferably to temperatures ranging from 90 °C to room temperature and optionally a part of distillate is distilled off, preferably under vacuum, at temperatures ranging from room temperature to 90 °C, preferably at 50 °C to 90 °C.

To the obtained solution which has optionally partly been distilled off, preferably under vacuum, isopropanol and water, subsequently and in arbitrary order, or a mixture thereof is added. In the preferred embodiment isopropanol is added first, followed by the addition of water to initialise crystallization.

The clear solution is cooled to temperatures from boiling temperature to 10 °C, and water is added to start crystallization. The product is then filtered off, washed with isopropanol, dried at room temperature under vacuum to the constant weight, and olanzapine water-isopropanol mixed solvate is obtained.

When the herein described olanzapine water-isopropanol mixed solvate is prepared from olanzapine in mother liquors containing, for example methylene chloride, or when it is prepared from the methylene chloride solvate form, the solvent is optionally distilled off and to the obtained solution which has optionally partly been distilled off, preferably under vacuum, isopropanol and water, subsequently and in arbitrary order, or a mixture thereof is added. In the preferred embodiment isopropanol is added first, followed by the addition of water to initialise crystallization, as above. After the crystallization is completed, the precipitate is filtered off and dried.

The olanzapine used as a starting material for the preparation of the described olanzapine water-isopropanol mixed solvate can also be crude olanzapine, or olanzapine in anhydrous or

any solvated or hydrated form, or mixtures thereof. Olanzapin is dissolved by heating in isopropanol and water, added subsequently and in arbitrary order, or a mixture thereof. In case that olanzapine is dissolved in water, isopropanol is added afterwards, and in case olanzapin is dissolved in isopropanol first, water is added afterwards. Both solvents can also additionally be added subsequently and in arbitrary order.

The clear solution is cooled to temperatures from boiling temperature to 10 °C, and water is added to start crystallization. The product is then filtered off, washed with isopropanol, dried at room temperature under vacuum to the constant weight, and olanzapine water-isopropanol mixed solvate is obtained.

The described olanzapine water-isopropanol mixed solvate prepared in any of the mentioned ways is of high quality and substantially free of impurities and can thus be used for the preparation of various other solvates, hydrates or mixtures thereof.

After the crystallization is completed, the precipitate is filtered off and dried. The obtained olanzapine water-isopropanol mixed solvate can optionally be recrystallized.

During the crystallization or precipitation procedure in any embodiment of the invention, optionally ethylenediaminetetraacetic acid disodium salt is added and after stirring, undissolved material is hot filtered.

For the preparation of form I, olanzapine water-isopropanol mixed solvate which was prepared in any of the above mentioned ways is then suspended in methylene chloride and heated until a clear solution is obtained. After the clear solution is obtained, a part of the solvent is evaporated under vacuum or optionally at atmospheric pressure or combination thereof at temperatures ranging from boiling point of the solution to -20 °C to isolate olanzapine methylene chloride solvate.

In another preferred embodiment olanzapine water-isopropanol mixed solvate is suspended in methylene chloride and heated to 35 °C to a clear solution and a drying agent, preferably Drierite (CaSO<sub>4</sub> anhydrous) is added.

Optional seeding with higher amounts of crystalline methylene chloride solvate is used.

To olanzapine methylene chloride solvate isopropanol is added at weight by volume ratio of 2 to 5, preferably 2 to 3, and the suspension is stirred at a temperature of 15 °C to 35 °C, in particular at room temperature, for 15 to 90 min, preferably from 30 to 60 min. Optional seeding with polymorph form I is used. Optionally methylene chloride solvate is suspended in isopropanol presaturated with olanzapine at weight by volume ratio of 2 to 30, preferably 3 to 15, and the suspension is stirred at a temperature of 5 °C to 50 °C, in particular at room temperature, for 15 to 90 min, preferably from 30 to 60 min. The product is filtered off and dried under vacuum at room temperature to the constant weight, then at 50 °C to the constant weight. Form I of olanzapine is isolated.

Processes known in prior art can also be used for the preparation of form I from the olanzapine water-isopropanol mixed solvate described herein.

The present invention is illustrated by the following Examples without being limited thereto.

## Preparation of olanzapine water-isopropanol mixed solvate

### Example 1

A mixture of 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride (26.6 g), 1-methylpiperazine (92 ml), dimethylsulfoxide (120 ml) and toluene (120 ml) was refluxed for 4 hours. The solution was cooled to 95 °C and 200 ml of distillate was distilled off under vacuum. The residue was cooled to room temperature, isopropanol (180 ml) was added, the solution was further cooled to 0 °C and water (36 ml) was added to initialize crystallization. After the crystallization completed the precipitate was filtered off and washed with isopropanol (20 ml). The wet product was suspended in isopropanol (200 ml) and heated to reflux to obtain a clear solution. Ethylenediaminetetraacetic acid disodium salt (3 g) was added and suspension was stirred for an hour. Undissolved material was hot filtered. The clear solution was cooled to 25 °C and water (6 ml) was added to start crystallization. The suspension was cooled to 0 °C, upon crystallization finished it was filtered off and washed with isopropanol (10 ml). The product was dried at room temperature under vacuum to the constant weight. Yield: 22.84 g. Loss on drying (140 °C): 13.6%. Water content (KF): 5.12%.

### Example 2

A mixture of 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride (26.6 g), 1-methylpiperazine (92 ml), dimethylsulfoxide (36 ml) and toluene (120 ml) was refluxed for 4 hours. The solution was cooled to 95 °C and 80 ml of distillate was distilled off under vacuum. The residue was cooled to room temperature, isopropanol (180 ml) was added, the solution was further cooled to 0 °C and water (36 ml) was added to initialize crystallization. After the crystallization completed the precipitate was filtered off and washed with isopropanol (20 ml). The wet product was suspended in isopropanol (200 ml) and heated to reflux to obtain a clear solution. Ethylenediaminetetraacetic acid disodium salt (3 g) was added and suspension was stirred for an hour. Undissolved material was hot filtered. The clear solution was cooled to 35 °C and water (6 ml) was added to start crystallization. The suspension was cooled to 0 °C, upon crystallization finished it was filtered off and washed with isopropanol (10 ml). The product was dried at room temperature under vacuum to the constant weight. Yield: 21.98 g. Loss on drying (140 °C): 13.2 %. Water content (KF): 5.09%. %. Assay of isopropanol (GC): 8.55 %.

Example 3

A mixture of 4-amino-2-methyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hydrochloride (26.6 g), 1-methylpiperazine (92 ml), dimethylsulfoxide (36 ml) and toluene (120 ml) was refluxed for 4 hours. The solution was cooled to 95 °C and 120 ml of distillate was distilled off under vacuum. The residue was cooled to room temperature, isopropanol (180 ml) was added, the solution was further cooled to 0 °C and water (36 ml) was added to initialize crystallization. After the crystallization completed the precipitate was filtered off and washed with isopropanol (20 ml). The wet product was suspended in isopropanol (200 ml) and heated to reflux to obtain a clear solution. Ethylenediaminetetraacetic acid disodium salt (3 g) was added and suspension was stirred for an hour. Undissolved material was hot filtered. The clear solution was cooled to 35 °C and water (6 ml) was added to start crystallization. The suspension was cooled to 0 °C, upon crystallization finished it was filtered off and washed with isopropanol (10 ml). The product was dried at room temperature under vacuum to the constant weight. Yield: 24.35 g. Loss on drying (140 °C): 13.5%. Water content (KF): 5.05%.

Example 4

Anhydrous olanzapine (10 g) was suspended in isopropanol (108 ml) and heated to reflux to obtain a clear solution. The solution was slowly cooled. At 57 °C water (6 ml) was added to start crystallization. The suspension was cooled to 0 °C, upon crystallization finished it was filtered off and washed with isopropanol (5 ml). The product was dried at room temperature under vacuum to the constant weight. Yield: 10.97 g. Loss on drying (140 °C): 13.3%. Water content (KF): 5.13%.

Example 5

Olanzapine obtained from mother liquors (60 g) was suspended in isopropanol (650 ml) and heated to reflux to obtain a clear solution. Ethylenediaminetetraacetic acid disodium salt (7.9 g) was added and suspension was stirred for an hour. Undissolved material was hot filtered. The clear solution was cooled to 25 °C and water (16 ml) was added to start crystallization. The suspension was cooled to 0 °C, upon crystallization finished it was filtered off and washed with isopropanol (50 ml). The product was dried at room temperature under vacuum

to the constant weight. Yield: 57.64 g. Loss on drying (140 °C): 13.5%. Water content (KF): 5.26%.

### **Preparation of olanzapine methylene chloride solvate**

#### Example 6

Olanzapine water-isopropanol mixed solvate (11 g) was suspended in methylene chloride (132 ml) and heated to obtain a clear solution. 66 ml of solvent was distilled off. Another 16 ml of methylene chloride was added and distilled off. The mixture was hot filtered and concentrated under vacuum to volume of 36 ml. During vacuum distillation the solution was cooled and product precipitated. The product was filtered off and dried under vacuum at room temperature to the constant weight. Yield: 8.47 g. Loss on drying (140°C): 12.7 %. Water content (KF): 0.40%.

#### Example 7

Olanzapine water-isopropanol mixed solvate (30 g) was suspended in methylene chloride (330 ml) and heated to 35°C to obtain a clear solution. Drierite (CaSO<sub>4</sub> anhydrous, 45 g) was added and stirred for an hour. The suspension was hot filtered and concentrated under vacuum to volume of 100 ml. During vacuum distillation the solution was cooled and product precipitated. The product was filtered off and dried under vacuum at room temperature to the constant weight. Yield: 21.31 g. Loss on drying (140°C): 11.3%. Water content (KF): 0.51%.

### **Preparation of olanzapin form I**

#### Example 8

Olanzapine methylene chloride solvate (10 g) was suspended in isopropanol (20 ml). The suspension was stirred at room temperature for an hour. The product was filtered off and dried under vacuum at room temperature to the constant weight, then at 50°C to the constant weight. Yield: 7.8 g.

#### Example 9

Olanzapine methylene chloride solvate (10 g) was suspended in isopropanol (150 ml, presaturated solution with olanzapine). The suspension was stirred at room temperature for



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one hour. The product was filtered off and dried under vacuum at room temperature to the constant weight, then at 50°C to the constant weight. Yield: 14.3 g

### Claims

1. An isopropanol/water mixed solvate of olanzapine which contains 2 molecules of water and one molecule of isopropanol per 2 molecules of olanzapine.
2. An isopropanol/water mixed solvate of olanzapine characterized by the x-ray structure in Figure 1.
3. An isopropanol/water mixed solvate of olanzapine characterized by the NMR spectra in Figure 2.
4. An isopropanol/water mixed solvate of olanzapine whose NMR spectra in  $\text{CDCl}_3$  are characterized by the following peaks at approximately 1.20 ppm, 2.20-2.40 ppm and 4.03 ppm.
5. Process for the preparation of isopropanol/water mixed solvate of olanzapine according to claim 1, wherein the solvent mixture for the preparation comprises isopropanol and water in a ratio 9 to 1 by volume.
6. Process according to claim 2, wherein the solvent mixture for the preparation comprises isopropanol and water in a ratio 20 to 1 by volume.
7. Process according to claim 2, wherein the solvent mixture for the preparation comprises isopropanol and water in a ratio 35 to 1 by volume.
8. Process for the preparation of isopropanol/water mixed solvate of olanzapine according to of claims 1, wherein the isopropanol/water mixed solvate of olanzapine is used in for the preparation of form I of olanzapine.
9. Process for the preparation of isopropanol/water mixed solvate of olanzapine according to of claims 1, wherein the isopropanol/water mixed solvate of olanzapine is used in for the preparation of any other solvate, hydrate forms of olanzapine, or mixtures thereof.
10. Process for the preparation of anhydrous forms of olanzapine wherein the isopropanol/water mixed solvate of olanzapine according to claim 1 is used.

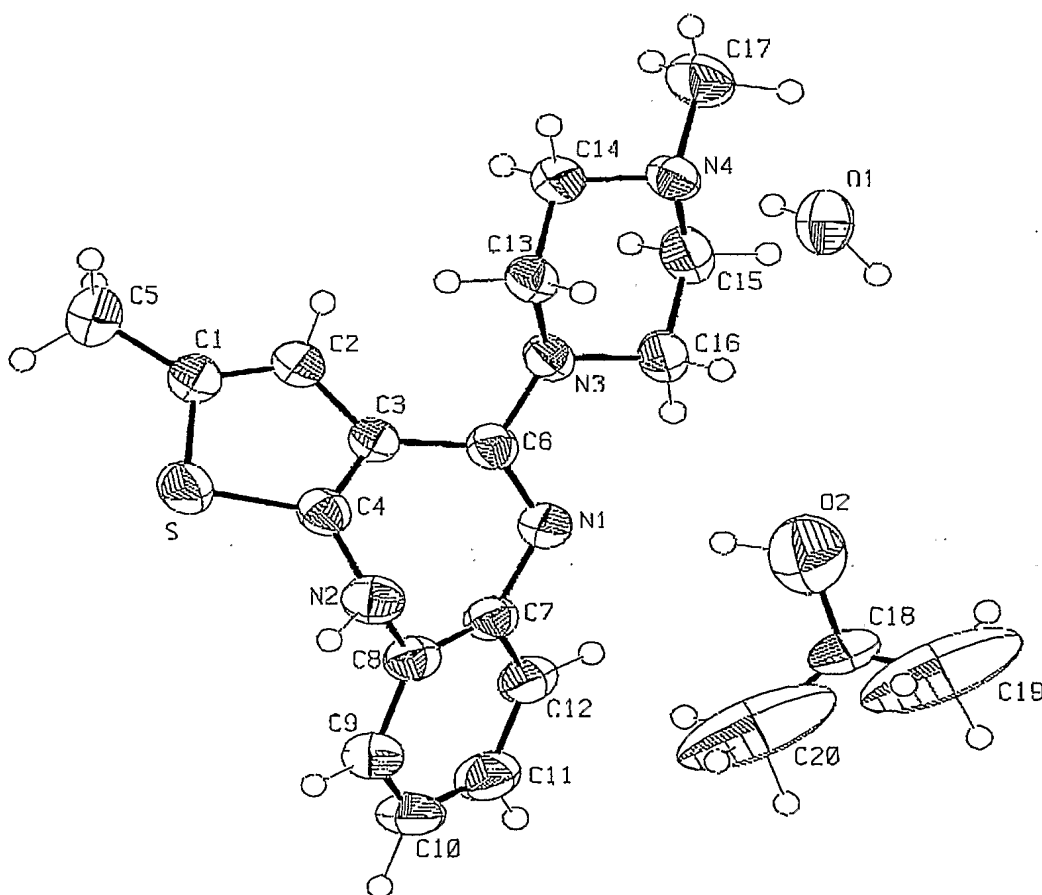


### Abstract

The invention relates to a novel and well defined solvate form of olanzapine which is characterized by the x-ray structure in Figure 1 and by the NMR spectra in Figure 2 and which contains 2 molecules of water and one molecule of isopropanol per 2 molecules of olanzapine. The olanzapine used as a starting material for the preparation of the described olanzapine water-isopropanol mixed solvate can be in any form, e. g. it can be used when it is contained in reaction solution, crude, in filtrate when various solvents are present, or in anhydrous or any solvated form. In the preferred embodiment the herein prepared and described olanzapine water-isopropanol mixed solvate is used for the preparation of form I of olanzapine.



1/2

**Fig. 1**

2/2

Fig. 2

